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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/925,731	08/10/2001	Monisola Adeokun	P 0282795 100135 US	4818

26161 7590 05/01/2003

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EXAMINER
SWITZER, JULIET CAROLINE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/925,731	ADEOKUN ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *3-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's amendments to claim 2 has been entered (see Amendment filed 1/21/2003). Claim 13 has been added. Claim 13 will be examined with the elected invention.

Election/Restrictions

2. Applicant's election with traverse of Group I, claims 1 and 2, particularly with regard to the SNP at position 2028 of SEQ ID NO: 1 is acknowledged. Applicants point out that claim 1 covers a method of detection involving determining the sequence at "at least one" of the twenty eight specified positions and that if the restriction requirement is allowed to stand it will limit applicants to claiming methods for determining the sequence at only one of the positions. This is not persuasive, nor is it necessarily accurate. Claims which particularly require the examination of more than one polymorphic site were not present when the restriction requirement was set forth. The claims, as presented and restricted, only **required** the determination of the sequence at a single polymorphic site. The current claim set includes claim 13 which requires the determination of the sequence present for all twenty-eight listed polymorphic sites. This claim is not separated from the elected polymorphism, but this does not remove the fact that claims which require only one of the polymorphisms are still restricted one from another. The restriction requirement was based on the claim set as presented, not a hypothetical claim set. Thus, since the claims requires only the sequencing of a single position, and all twenty-eight of the recited positions are independent and distinct from one another and the search and examination of all twenty-eight separately would pose a significant burden to the examiner, the requirement that applicant select a single polymorphism for examination is proper and maintained. Claim 13 will be examined within the elected invention because it is within the scope of the elected invention.

The requirement is therefore made FINAL.

Specification

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Detection of Polymorphisms in the Human OATPC Gene.

Priority

4. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claim 13 of this application. The priority document does not disclose all of the polymorphisms recited and required in claims 1, 2 and 13. Claims 1 and 2 are considered to have descriptive support for the elected invention insofar as the elected invention requires the diagnosis of a polymorphism present at position 2028 of instant SEQ ID NO: 1 as the provisional application discloses this polymorphism and the detection of this polymorphism. However, as currently written, the claims are being interpreted as requiring the analysis of AT LEAST position 2028 of and any of the other recited positions, all of which are not supported in the provisional application.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 2 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2 and 13 are is indefinite over the recitation "determining the sequence of the human at at least one of the following polymorphic positions..." for the following reasons:

First, the claim language is unclear because it requires determining the sequence "of the human" and it is not clear how to determine the sequence of a human. Second, the word "sequence" implies the determination of the nucleotide present at more than one position of a nucleic acid, yet the claims set forth that the sequence is determined at a minimum of one of the recited positions. It is not clear how a sequence can be determined at a particular position. Amendment of the claim to recite, for example, "determining the nucleotide present at position 2028 in a sequence of the OATPC gene as defined by the position in SEQ ID NO: 1" would obviate this rejection. Claims 2 and 13 are also indefinite for these reasons because they depend from claim 1 but do not clarify the issues.

Claim 2 is indefinite over the recitation "using the sequence of the human at at least one of the polymorphic positions" because it is not clear if the claim is requiring the use of the nucleic acid sequence itself (i.e. the molecule) or if the claim is attempting to delineate the use of some sort of information gleaned from the method of claim 1 in a further analysis.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-2 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting and sequencing the human OATPC gene and portions thereof, does not reasonably provide enablement for methods which are limited to the detection of a polymorphism at position 2028 in a sequence of the OATPC gene as defined by the position in SEQ ID NO: 1. Furthermore, the specification does not provide enablement for methods in a sequence of the human is used to assess the pharmacogenetics of a drug transportable by OATPC. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims

This rejection applies to the instant claims insofar as they might be interpreted as methods for the detection of the presence or absence of particular single nucleotide polymorphisms. It applies to claim 2 insofar as the claim implies that there would be a discernable pharmacogenetic interaction between one or all of the recited polymorphisms and a drug transportable by OATPC. Insofar as the instant claims read generally on methods for sequencing the human OATPC gene, this rejection does not apply. The teachings of the specification (at, e.g., pages 14-18) and of the prior art as exemplified by Abe et al. disclose

methods of detecting and sequencing the OATPC gene and portions thereof. Such methods are encompassed by the instant claims as written, and a person skilled in the art could clearly practice methods of detecting and sequencing a known gene without further guidance. However, it is unpredictable as to whether one of skill in the art could use without undue experimentation methods requiring detection of the polymorphism at position 2028 in a sequence of the OATPC gene as defined by the position in SEQ ID NO: 1 or methods for pharmacogenetic analysis which comprise detection of the polymorphism at position 2028 in a sequence of the OATPC gene as defined by the position in SEQ ID NO: 1, which methods are also encompassed by the claims. Furthermore, it is unpredictable as to whether one of skill in the art could use without undue experimentation a method which requires the examination of twenty eight different single nucleotide polymorphisms in the OATPC gene.

It is noted that the instant claims each recite methods which comprise the detection of nucleotide sequences at at least one of twenty eight different polymorphic sites. A restriction requirement was set forth in which applicant was required to select a single polymorphic site for examination. Applicant selected the polymorphism at position 2028 in a sequence of the OATPC gene as defined by the position in SEQ ID NO: 1. This enablement rejection considers only this site in the claims that recite polymorphisms in the alternative. With regard to claim 13, many of the examples in this rejection are directed at the elected polymorphism, but it is to be understood that the rejection applies to claim 13 also which requires the examination of twenty eight different polymorphic sites.

The instant claims are drawn to methods for the detection of a polymorphism in an OATPC gene in a human. The methods comprise steps in which the particular nucleotide is

detected at a particular position in different portions of the human OATPC gene. Claim 2 further requires a step in which pharmacogenetic analysis is carried out.

State of the Prior Art

The prior art teaches some polymorphisms in the human OATPC gene (see for example Laubert *et al.* (WO 00/08157) and Tamai *et al.* (Biochemical and Biophysical Research Communcations 273, 251-260, 2000). However, neither of these provide any characterization of the how these polymorphisms effect the activity of the OATPC encoded polypeptide. The prior art does not provide specific guidance with regard to the polymorphism identified herein as being at position 2028 in a sequence of the OATPC gene as defined by the position in SEQ ID NO: 1, or any of the other polymorphism identified herein, whose examination is required by claim 13.

Level of Unpredictability and Skill in the Prior Art

There is also a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state, a physiological state, or the processing of a drug (i.e. pharmacogenetics). For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a

particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

Indeed, the post filing date art, for example Tirona *et al.* (The Journal of Biological Chemistry, Vol. 276, No. 38, pages 35669-35675) and Nozawa *et al.* (The Journal of Pharmacology and Experimental Therapeutics, 2003, Vol. 302, No. 2, pages 804-813) further underscores the unpredictability of attempts to associate single nucleotide polymorphisms with functional activity of OATPC. For example, Nozawa *et al.* were not able to detect any significant alteration in the transport activity of OATPC associated with four different single nucleotide polymorphisms. Tirona *et al.* found that only half of the fourteen polymorphisms they screened were functionally relevant for OATPC activity.

The level of skill in the pertinent art is quite high, i.e. generally a PhD in biochemistry, but the unpredictability in the art is higher. While the instant specification has disclosed a number of different polymorphisms in the OATPC gene, it remains highly unpredictable as to the biological significance of these polymorphisms. While the specification teaches that the elected polymorphism results in an amino acid substitution in the encoded OATPC polypeptide, the specification is silent as to how this truncation effects the functioning of the encoded polypeptide. Thus, the claimed method directed towards the detection of polymorphisms, or pharmacogenetic analysis following polymorphism detection, for enablement of the full scope, requires the knowledge of unpredictable and potentially non-existent associations between the instantly elected polymorphism and some phenotypic or activity trait. Even if the elected polymorphism is in some way associated with some disease or has an effect on the ability of OATPC to transport a substrate, it is difficult (if not impossible) to know or predict from the teachings of the specification which disease or substrates would be effected or how the polymorphism is associated. That is, it is unpredictable as to whether the presence of a particular allele the polymorphism would confer a higher or lower likelihood of having the disease or higher or lower transport activity of a given substrate. In this case, the possible uses for the claimed methods are undefined, beyond the suggestion that they can be used to detect a disease or an activity associated with the OATPC gene prior to treatment with a OATPC drug.

Direction Provided in the Specification and Working Examples

The specification teaches that the polypeptide encoded by the OATPC gene is involved in multifunctional transport of organic anions, and in particular has been demonstrated to be

involved in the transport of some xenobiotics and statins, as well as thryroid hormones and conjugated steroids. Further, the specification provides 24 polymorphisms in the OATPC gene, 4 of which result in amino acid changes. In particular, the specification teaches a polymorphic site at position 2028 in a sequence of the OATPC gene as defined by the position in SEQ ID NO: 1, located in exon 14 of the OATPC gene. The polymorphism is a single nucleotide polymorphism which results a substitution of leucine for phenylalanine in the expressed protein (p. 14 of the specification). The specification is silent with respect to the effect of this polymorphism on the biological activity of the OATPC gene, beyond the fact that it results in an amino acid substitution. The specification does not discuss or demonstrate how this truncation effects the activity of the encoded polypeptide nor does the specification discuss or demonstrate the effect of any of the other eight recited polymorphisms on the biological activity of the gene. The specification does not disclose any relationship between the presence of this polymorphism a change in the activity or expression of the OATPC or between the presence of a particular allele of this polymorphism and any particular disease state or physiological condition.

The amount of direction or guidance presented in the specification with regard to how to use the instant invention is minimal. With regard to claims directed towards simple detecting the presence of the gene polymorphism, applicant speculates that "one approach is to use knowledge of polymorphisms to help identify patients most suited to therapy with particular agents (this is termed "pharmacogenetics") (p. 2)," but the specification does not elucidate the particular effects of any of the instantly disclosed polymorphisms on a response to drug therapy. Since the effects of any given polymorphism on gene activity are highly unpredictable, it is impossible to predict from the teachings of the instant specification what identifications can be made using the

instantly claimed methods. That is, the specification does not provide any guidance as to how the polymorphism at position 2028 in a sequence of the OATPC gene as defined by the position in SEQ ID NO: 1 would be associated with any pharmaceutical agent. The specification does not discuss whether this particular polymorphism will increase the likelihood of a positive or negative response to any drug. Furthermore, with regard to claim 13, which recites a method of treatment of a OATPC disease, the specification does not provide any guidance as to what disease is in fact associated with the presence or absence of the polymorphism at position 2028 in a sequence of the OATPC gene as defined by the position in SEQ ID NO: 1, other than the suggestion that these methods could be carried out for "OATPC mediated diseases." The specification further fails to provide any guidance as to the appropriated OATPC drug to be administered after the detection of the polymorphism, or the desired effect of administration of the drug (i.e. to up or down regulate the activity of the gene, and how either of these is to be accomplished). The specification provides no guidance or working examples that teach or demonstrate the ability to use the disclosed polymorphic site as a marker for any disease in particular, or for disease in general, or how to use to assess the pharmacogenetics of a drug transportable by OATPC.

Quantity of Experimentation

The quantity of experimentation required to discover how to use the instant invention is very high. In order to use the claimed invention, one would have to establish a relationship between the polymorphism at nucleotide 2028 in a sequence of the OATPC gene as defined by the position in SEQ ID NO: 1 some physiological or disease state or any one of the many

possible drugs that are transportable by OATPC. Indeed, even to use the method of claim 1 to identify patients suited for particular pharmaceutical agents, one would need to know that the polymorphism at nucleotide 2028 in a sequence of the OATPC gene as defined by the position in SEQ ID NO: 1 was in some way associated with response to some pharmaceutical agent. In order to obtain the type of information necessary to practice the claimed invention, one would be required to undertake the screening of hundreds or thousands of patients as well as possible hundreds of diseases or pharmaceutical agents. Even if such experiments were undertaken, it would still be unpredictable as to whether any associations would be detected, in light of the unpredictability of such associations, as already discussed. Thus, while one could perform further research to determine whether applicant's method would be useful in disease detection and/or treatment and/or predicting response to drugs, it is unknown as to what the outcome of such research might be and as to whether any quantity of experimentation would result in the identification of an association between the polymorphisms at position 2028 of SEQ ID NO: 1 and any disease or condition or particular drug. Further, absent a teaching that the polymorphism at position 2028 of SEQ ID NO: 1 is not associated with such conditions or responses, it is further unpredictable as to whether detection of the polymorphism would be useful in predicting, e.g., a patient's response to drugs transportable by OATPC.

Furthermore, it is noted that the practice of the invention of claim 2 requires the using the sequence to assess pharmacogenetics of a drug transportable by OATPC. The specification teaches that OATPC has been demonstrated to be involved in the transport of some xenobiotics and statins, as well as thryroid hormones and conjugated steroids. However, the specification does not disclose a relationship between the transport of any with these drugs and the

polymorphism at position 2028 in a sequence of the OATPC gene as defined by the position in SEQ ID NO: 1. The identification of a relationship between and the elected polymorphism would be highly unpredictable, requiring an extensive amount of research and experimentation. Furthermore, the scope of the claims includes the assessment of a possible relationship or the knowledge of a possible relationship between the OATPC polymorphisms and any number of hundreds of thousands of possible drugs that may be transported by this anionic transporter that is produced in the liver.

Thus, in light of the nature of the invention, the state of the art, the high level of unpredictability in the art, the lack of direction or working examples in the specification, and the high quantity of experimentation that would be required to practice the claimed invention, it is concluded that undue experimentation would be required to use the instantly claimed invention. Thus, with respect to claims 1-2 and 13, although the specification certainly enables one to detect the presence of the polymorphism(s) (i.e. the "make" portion of 112 1st paragraph), it would require undue experimentation in order to determine how to use the methods of claims 1-2 and 13. Considering all of the factors discussed herein, it is concluded that it would require undue experimentation to determine the particular drugs whose transport would be effected by any of the polymorphisms taught in the instant specification, let the elected polymorphism, and thus to practice the claimed invention commensurate in scope with the present claims.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Abe et al. (The Journal of Biological Chemistry, Vol. 274, No. 24, pp. 17159-17163).

Abe et al. teach a method for the detection of a polymorphism in a OATPC gene in a human which comprises determining the sequence of the nucleic acid of the human at position 2028 of the OATPC gene as defined by the position in instant SEQ ID NO: 1. Specifically, Abe et al. teach a wherein the OATPC gene is sequenced (p. 17159). At least nucleotides the nucleotides 100-2175 of instant SEQ ID NO: 1 are identical to nucleotides 1-2076 of the nucleic acid sequenced by Abe *et al.* (see attached alignment), thus encompassing the position 2028 in a sequence of the OATPC gene as defined by the position in SEQ ID NO: 1. Furthermore, Abe *et al.* use the nucleotide sequence to assess the pharmacogenetics of the expressed OATPC gene in Xenopus oocytes (p. 17160-17161). This reference is considered to teach the invention of claims 1 because the method contains only a single method step, one in which the sequence at position 2028 in a sequence of the OATPC gene as defined by the position in SEQ ID NO: 1 is determined (i.e. which is inherently accomplished by sequencing the portion of the gene that overlaps with position 2028 in a sequence of the OATPC gene as defined by the position in SEQ ID NO: 1). Furthermore, with regard to claim 2, Abe *et al.* use the sequence of the human (at all of the positions within the gene, including the polymorphic position) to asses the pharmacogenetics of a drug transportable by OATPC.

11. Claims 1 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Koning *et al.* (The Journal of Biological Chemistry, July 2000, Vol. 275, No. 30, pages 23161-23168).

Koning *et al.* screen a genomic database to identify a cosmid clone containing the genomic sequence of the OATPC (referred to therein as OATP2) transporter, and complete an analysis of the genomic structure of the OATPC gene (p. 23164). Koning *et al.* teach that cosmid AC022335 contains the entire genomic DNA of the OATPC gene. Thus, by studying the sequence of the genomic clone, Koning *et al.* have determined the nucleotide present at every one of the nucleic acid positions recited in instant claim 13. Furthermore, Koning *et al.* provide the amino acid sequence of the OATPC polypeptide (Fig. 1, B) and have therefore determined the amino acid present at each of the polymorphic sites recited for instant SEQ ID NO: 2. Therefore, the teachings of Koning *et al.* inherently meet the limitations of claims 1 and 13 which encompass any methods wherein the nucleotide sequence of the OATPC genomic DNA is "determined" and the polypeptide sequence is also determined.

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

Juliet C. Switzer
Examiner
Art Unit 1634

April 28, 2003